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Implementation of a Metrology Programme to provide traceability for Radionuclides Activity measurements in the CNEN Radiopharmaceuticals Producers Centers

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ABSTRACT

The commercialization and use of radiopharmaceuticals in Brazil are regulated by *Agência Nacional de Vigilância Sanitária* (ANVISA) which require Good Manufacturing Practices (GMP) certification for Radiopharmaceuticals Producer Centers. Quality Assurance Program should implement the GMP standards to ensure radiopharmaceuticals have requirements quality to proving its efficiency. Several aspects should be controlled within the Quality Assurance Programs, and one of them is the traceability of the Radionuclides Activity Measurement in radiopharmaceuticals doses. The quality assurance of activity measurements is fundamental to maintain both the efficiency of the nuclear medicine procedures and patient and exposed occupationally individuals safety. The radiation doses received by patients, during the nuclear medicine procedures, is estimated according to administered radiopharmaceuticals quantity. Therefore it is very important either the activity measurements performed in radiopharmaceuticals producer centers (RPC) as the measurements performed in nuclear medicine services are traceable to national standards. This paper aims to present an implementation program to provide traceability to radionuclides activity measurements performed in the dose calibrators (well type ionization chambers) used in Radiopharmaceuticals Producer Center placed in different states in Brazil. The proposed program is based on the principles of GMP and ISO 17025 standards. According to dose calibrator performance, the RPC will be able to provide consistent, safe and effective radioactivity measurement to the nuclear medicine services.

1. INTRODUCTION

The procedures using radiopharmaceuticals continue to be a growing area in medicine. The radiopharmaceuticals are administered to patients in Nuclear Medicine Services (NMS) for therapy or diagnosis of cardiac diseases, neurological disorders and many others, but mainly cancer. The nuclear medicine procedures are controlled in order to ensure the radiological safety of patients and exposed occupationally individuals. In Brazil, ANVISA established the requirements for radiopharmaceutical production and application according to Good Manufacturing Practice [1],[2], and the Nuclear Energy National Commission (CNEN) keeps the responsibility to manage the facilities and procedures using radioactive materials according the international recommendations [3].

It is very important each process be conducted within the framework of a quality assurance program to achieve radiopharmaceuticals effectiveness [3]. The safe and quality of the nuclear medicine procedures requires that the amount of radiation delivered to the patient be determined as accurately and consistently as possible. The radiation dose delivered with unsealed sources is difficult to measure directly. This is due to the fact that the source of the radiation is internal to the patient and is much more diffuse. Moreover, the distribution of the radiation source (the radioactive drug) can be variable between patients, depending upon individual metabolism. Rather than try to measure the dose to the tumors and to the critical organs, it is necessary to control the amount of injected activity in a nuclear medicine procedures [4]. Therefore, it is very important the RPC provide reliable activity measurements of the radiopharmaceuticals dose to NMS and the measurements must be traceable to national and international standards [4]. The dose calibrator is the instrument used both by RPC as NMS, to measure the activity of the radionuclide which is present in the radiopharmaceuticals doses. According to Radiopharmaceuticals GMP standardization, this instruments must be calibrated by the Metrologic National Authority [5].

The National Laboratory for Ionizing Radiation Metrology (LNMRI) placed in Radioprotection and Dosimetry Institute (IRD) was designated by *InMetro* as metrology national laboratory in the field of ionizing radiation. LNMRI holds the national standards and one of their responsibilities is to disseminate standards to users in the field of nuclear medicine [6][7].

In the nuclear medicine field, the manner to obtain instruments calibrations is the establishment of comparison programs coordinated by Metrologic National Authorities. Comparison Programs is a common practice between NMS and LNMRI since 1998 in Brazil [6]. And now, it to ensure the quality of the activity measurements, a comparison program need to implemented between LNMRI and RPC.

There are four Brazilians RPC belonging to CNEN, which supply radiopharmaceutical to several NMS´s. These RPC´s are placed in different states around the country.

This work aimed the implementation of a national comparison program between RPC and LNMRI to ensure the traceability of the activity measurements performed in dose calibrators used by RPC since the activity of the radiopharmaceuticals must be determined as accurately as possible, according to ANVISA and CNEN requirements. These requirements are based on the principle: the radiopharmaceutical administrated must be sufficient to ensure the effectiveness of the diagnosis and treatment since had been maintained the radiologic safety of the workers and patients.

2. METHODOLOGY

Before the comparison, the LNMRI requires the RPC demonstrate that their dose calibrators have been tested according some aspects recommended by CNEN N.N 3.05 standard (accuracy 10%, precision 5%, reproducibility 5% and linearity 20% using ^{133}Ba, ^{60}Co and ^{137}Cs calibrated sources) [8]. Furthermore, the RPC must be demonstrate, by gamma spectrometry analysis, the radiopharmaceuticals have been produced with impurities level according to proposed limits by European Pharmacopeia.

The first Comparison has been performed between Nuclear Engineering Institute (IEN) and LNMRI, both placed in Rio de Janeiro. ^{18}F was the first radionuclide used in comparison, which is produced routinely by IEN in the form 2-[^{18}F]-fluoro-2-deoxyglucose (^{18}FDG). The samples containing ^{18}F radionuclides were contained in a 20 mL glass vials. The ^{18}F sample was diluted with ultrapure water in a 10 mL sufficient volume. The activity was measured in

dose calibrator *Capintec CRC ULTRA* placed in the hot cell of radiopharmaceutical Production. The radiopharmaceuticals producer was asked to make three measurements. In the next step, the same ^{18}F sample vials have been sent to LNMRI. The vials geometries correspond that routinely used for activity measurements in the hospitals. At the LNMRI, the samples were measured both in a *Capintec CRC-15R* work standard chamber as in the *Centronic IG-11* secondary standard chamber. The *Capintec CRC-15R* is calibrated by the *Centronic IG-11* secondary standard ionization chamber, which in turn, is previously calibrated by primary standardization $4\pi\beta-\gamma$ coincidence systems. The geometry used for comparison has been calibrated both ionizations chambers *Centronic IG-11* as the *Capintec CRC-15R*. All the measurements were corrected to a reference date and the ^{18}F half-lives considered were 1.82 h.

The criteria to analyze the performance is the Ratio, R, calculated as

$$R = \frac{\bar{X}}{X_{ref}} \qquad (1)$$

where $\bar{X}$ is the RPC result and X_{ref} is the LNMRI result. The acceptance criteria adopted for RPC was $0.97 < R < 1.03$.
The uncertainties were evaluated according to ISO GUM (International Organization for Standardisation) [8], and in this work, they are quotes as standard uncertainties with a coverage factor of $k = 2$ providing a confidence level of 95%.

3. RESULTS AND DISCUSSIONS

The Quality Control Test required in CNEN N.N. 3.05 standard for dose calibrators used in nuclear medicine, demonstrated the *Capintec CRC ULTRA* Dose calibrator used for ^{18}F activity measurements have a good performance. The results for accuracy and precision are showed in table 1. The linearity test was performed by the decaying source method utilizing a ^{18}F source with an initial activity of 59.7mCi (2.21 GBq). The agreement between the experimental data and theoretical values demonstrated that the *Capintec CRC ULTRA* Dose calibrator presents a linear response over the range of activities used in routine measurements. Considering each individual measurement, the percentage error is in the range of 0.01 % up to 0.87%, complied with CNEN acceptance limit of 20% (CNEN, 1996). Deviation from linearity for *Capintec Ultra* is presented in figure 1.

Table 1: Quality Control results for *Capintec Ultra* Dose Calibrator. Tests required in normative regulatory CNEN N.N. 3.05.

Calibrated Source	**^{60}Co**	**^{133}Ba**	**^{137}Cs**
Accuracy (%)	2.20	1.28	0.75
Precision (%)	0.19	0.03	0.14

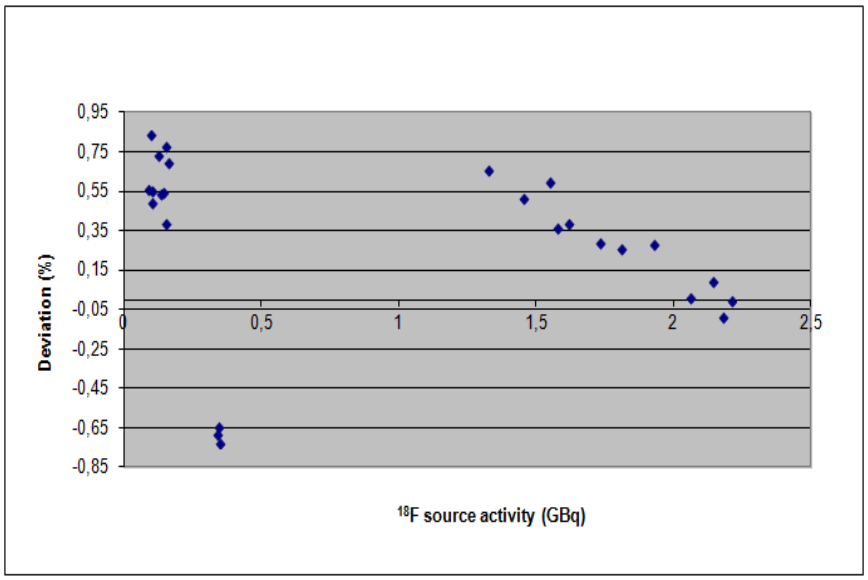

Figure 1: Linearity test resulto for *Capintec Ultra* dose calibrator

3.1. Comparison with LNMRI of the ^{18}F activity measurements

The ^{18}F activities measured in IEN and LNMRI were 78.29 MBq and 78.8 MBq respectively. These results are corrected to a same reference date. Therefore, the Ratio R found is 0.9935 and it domonstrates that ^{18}F activities measurements performed in the *Capintec CRC - Ultra* dose calibrator are according to acceptance criteria adopted. It can be considerate the instruments presented a good performance in the comparison.

3.2. Uncertainity

The uncertainity components for the calibration factor of the ^{18}F acitiviy measurements are given in table 2. The dominant unctertain contributor was calibration factor for the secondary standard chamber. The uncertainty expanded (k = 2) calculated was 3.8%.

Table 2: Uncertainity Components for the calibration factor for ^{18}F(FDG) in the comparison

Uncertainity Component	Standard uncertainty components (%)	
	Type A	Type B (%)
Calibration factor for the secondary standard chamber		1.62
Standard Deviation of mean of activity sample measured in CRC Ultra (IEN)	0.18	
Half-life of ^{18}F		0.02
Non linearity of the chamber		0.87
Digital Visor Resolution of the Capintec CRC - Ultra		0.0003
Volume sample		0.5
Combined standard uncertainty	1.91	
Expanded Uncertainity (k = 2)	3.82	

3. CONCLUSIONS

The comparison program of activity measurements was established between IEN (RPC) and LNMRI. It was possible evaluated the accuracy and performance of dose calibrator for ^{18}F activity measurements (*Capintec CRC ultra*). The results showed that the instrument meets the criteria established for a good performance of the ^{18}F activity measurements.
The establishment of comparison programs of activity measurements between RPC and LNMRI is an important tool to ensure the satisfactory performance of radionuclide calibrators used in RPC. Firstly this program was established for ^{18}F between IEN-CNEN (Rio de Janeiro) and LNMRI, but in the next steps, will be established also between other CNEN Radiopharmaceuticals Producer Centers placed in other brazilians states (IPEN, CDTN e CRCN), and for all radionuclides manufactured in each RPC separatelly.

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